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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 42-67 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 42-67 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 01.23.04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-41 have been cancelled.

Claims 42-67 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities: The first line of the specification states that the instant application claims priority to U.S. Application Serial No. 09/337,619 (now allowed), which needs to be updated to add the U.S. Patent number.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 42-58, 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied

through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (see MPEP 2164).

In the instant case, the claims encompass a method for treating cancer, comprising administering to a subject an effective amount of a stabilized CpG immunostimulatory oligonucleotide, further comprising administering a chemotherapeutic agent, further comprising administering a cancer immunotherapeutic agent, wherein the cancer is brain cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, leukemia, carcinoma, sarcoma. Therefore, the claims encompass a genus of possibly millions of different nucleic acids considering every possible CpG-containing oligonucleotide, including many chemotherapeutic and immunotherapeutic agents that may be effective in cancer treatment. The specification indicates one sub-genus of CpG containing oligonucleotides, which comprise an unmethylated CpG motif represented by the formula 5'-$X_1X_2CGX_3X_4$-3', thus, indicating distinct structural and functional properties of one sub-genus of molecules embraced by the claims. However, as mentioned above, the claims encompass any CpG containing oligonucleotide, chemotherapeutic and immunotherapeutic agents. Therefore, the claims encompass a number of sub-genuses of CpG containing oligonucleotides such as antisense oligonucleotides and methylated CpG containing oligonucleotides as well

as others, in addition to many chemotherapeutic and immunotherapeutic agents that are well known in the art.

Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function" and the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity and which therefore, fails to satisfy the written description requirement. Similarly, a CpG-containing oligonucleotide, a chemotherapeutic and a immunotherapeutic agent as claimed does not distinguish CpG-containing oligonucleotides, chemotherapeutic and immunotherapeutic agents from others having the same activity or function and as such, does not satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Thus, it is impossible to predict which CpG-containing oligonucleotides would be effective at treating cancer, wherein the cancer is brain cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, leukemia, carcinoma and

sarcoma. Therefore, the claims encompass CpG-containing oligonucleotides, which are not defined in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Further, there is no written description for any species of CpG-containing oligonucleotide, which would be effective at treating cancer.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

5. Claims 42-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 42-67 are drawn to a method for treating cancer, comprising administering to a subject an effective amount of a stabilized CpG immunostimulatory oligonucleotide, further comprising administering a chemotherapeutic agent, further comprising administering a cancer immunotherapeutic agent, wherein the cancer is

brain cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, colon cancer, leukemia, carcinoma, sarcoma; wherein atleast one nucleotide has a phosphate backbone modification, wherein the oligonucleotide has 8 to 100 nucleotides, further wherein the phosphate backbone is a phosphorothioate modification, wherein the oligonucleotide includes the phosphate backbone modification on the 5' inter-nucleotide linkages, 3' inter-nucleotide linkages, further wherein the oligonucleotide comprises 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, wherein X_1X_2 and X_3X_4 are nucleotides, and wherein the sequence is not palindromic, further wherein X_1X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApG, CpT, CpG, TpA, TpT, and TpG; and X_3X_4 are nucleotides selected from the group consisting of: TpT, CpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA, further wherein X_1X_2 are GpA and X_3X_4 are TpT, further wherein X_1X_2 are both purines and X_3X_4 are both pyrimidines, further wherein X_1X_2 are GpA and X_3X_4 are pyrimidines, further wherein the oligonucleotide is 8 to 40 nucleotides in length. further wherein 5' $X_1X_2CGX_3X_4$ 3' is not palindromic, further wherein the CpG immunostimulatory oligonucleotide includes at least two CpG motifs, further wherein at least one of the at least two CpG motifs is not palindromic. However, the specification provides insufficient guidance and objective evidence that such stabilized CpG immunostimulatory oligonucleotide would predictably treat cancer. The specification provides no guidance on the administration of the claimed oligonucleotide in vivo.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The nature of the invention:

The claims have been described supra. Therefore the general nature of the invention is cancer therapy comprising administering to a subject an effective amount of a stabilized CpG immunostimulatory oligonucleotide, further comprising administering a chemotherapeutic and/or a immunotherapeutic agent.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass any stabilized CpG-containing oligonucleotide and any chemotherapeutic and/or immunotherapeutic agents.

The unpredictability of the art and the state of the prior art:

It is noted that the claims encompasses a method for treating cancer comprising administering any stabilized CpG-containing oligonucleotide to a subject, thus the claims embrace a multitude of CpG-containing oligonucleotides that have 8-100 nucleotides in length and have a phosphate backbone modification which is a phosphorothioate or phosphorodithioate modification.

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule.

For instance, Agarwal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (see page 119 "concluding remarks" in particular).

Similarly, Crooke et al. (Therapeutic application of Nucleotides, R.G. Landers Co., Austin, TX, 1995, Chapter 5, pages 63-84) phosphorothioate nucleotides clearly have significant limits (see page 79 table 5.2, in particular): pharmacodynamically, they have relatively low affinity per nucleotide unit, pharmacokinetically, phosphorothioates do not cross blood brain barrier, are not significantly orally bioavailable and may display dose-dependent pharmacokinetics. Toxicologically, clearly the release of cytokines, activation of complement and interference with clotting will pose dose limits if they are encountered in the clinic.

Working Examples and Guidance in the Specification

The specification has no working examples indicating any CpG immunostimulatory oligonucleotide comprising an unmethylated CpG motif can be useful for treating any kind of cancer.

Quantitv of Experimentation

Considering the breadth of the claims and lack of working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention with a reasonable expectation of success. Considering the teaching in the art and lack of examples and guidance in the specification, one of skill in the art could not use the claimed CpG-containing oligonulceotides comprising at least one unmethylated CpG motif and has a phosphorothioate or a phosphorodithioate modified backbone. However, additional experimentation would be required in order to use any CpG-containing oligonucleotide that does not specifically have these characteristics to treat or prevent any type of cancer. For instance, one would have to show how a CpG-containing oligonucleotide could function as immunostimulatory molecules. The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonulceotides would not work for treating or preventing any cancer.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide; 2) the breadth of the

claims as mentioned above; 3) the limited number of working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed vaccine composition is undue.

Thus, The instant application gives no data relevant to the use of the nucleic acids mentioned in the claims in any in vivo method to control or affect any of the conditions mentioned in the claims. One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 47-65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6653292 (Krieg and Weiner). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons as set forth.

Claims have been described supra.

Claims 1-22 of U.S. Patent No. 6653292 (Krieg and Weiner) are drawn to a method of increasing the responsiveness of a cancer cell to a cancer therapy using an immunomodulatory nucleic acid as compared to the absence of the immunostimulatory nucleic acid, comprising administering to a subject having cancer an effective amount for increasing the responsiveness of a cancer cell to a cancer therapy of an immunostimulatory nucleic acid, comprising 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, wherein X_1X_2 and X_3X_4 are nucleotides, and wherein the sequence is not palindromic, further wherein X_1X_2 are nucleotides selected from the group consisting of: GpT, GpG, GpA, ApA, ApG, CpT, CpG, TpA, TpT, and TpG; and X_3X_4 are nucleotides selected from the group consisting of: TpT, CpT, ApT, TpG, ApG, CpG, TpC, ApC, CpC, TpA, ApA, and CpA, further wherein X_1X_2 are GpA and X_3X_4 are TpT, further wherein X_1X_2 are both purines and X_3X_4 are both pyrimidines, further wherein X_1X_2 are GpA and X_3X_4 are pyrimidines, further wherein the oligonucleotide is 8 to 40 nucleotides in length. Further, since claims 1 and 18-22 of U.S. Patent No. 6653292 teach a species comprising within the genus of claim 1 of the instant application, claims 1-22 would anticipate the methods of claims 47-65 of the instant application.

Thus, the claims 1-22 of U.S. Patent No. 6653292 (Krieg and Weiner) anticipate the instant claims.

Conclusion

7. No claims are allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

9. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789